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Anh Nguyen
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To: NCIC HPV@EPA
cc:
Subject: Fw: Environmental Defense comments on the Pyridine and Pyridine Derivatives category

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05/17/2004 11:30 AM

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Subject: Environmental Defense comments on the Pyridine and Pyridine Derivatives category

(Submitted via Internet 5/17/04 to oppt.ncic@epa.gov, hpv.chemrtk@epa.gov, boswell.karen@epa.gov, chem.rtk@epa.gov, lucierg@msn.com and laurie_miller@americanchemistry.com)

Environmental Defense appreciates this opportunity to submit comments on the robust summary/test plan for the Pyridine and Pyridine Derivatives category.

The test plan and robust summaries for pyridine and pyridine derivatives was submitted by the Pyridine and Pyridine Derivatives HPV Work Group of the American Chemistry Council. This is a proposal for a category comprised of nine members.

The test plan and robust summaries are long and complex, and the justification for a single category is far from convincing. There are significant structural differences among the proposed members, a common mechanism of action has not been identified or proposed, and the available data indicate large qualitative as well as quantitative differences in toxicological properties. Hence we cannot support the category as proposed.

Although we do not support establishment of a single category for the pyridine and pyridine derivatives, we do recommend that four submissions (two for single compounds and two for categories) for the nine chemicals would be consistent with the available science. Our recommended categories are as follows:

1. piperidine (110-89-4)
2. pyridine (110-86-1), 4-picoline (108-89-4), 3-picoline (108-99-6), 2-picoline (109-06-8) and pyridine alkyl ethers (68391-11-7)
3. pyridinium (68909-18-2)
4. nicotinonitrile (100-54-9) and picolinonitrile (100-70-9)

Additional testing beyond that recommended by the sponsor in the test plan will be necessary to accommodate HPV requirements for these four submissions. In particular, the full range of environmental fate and ecotoxicity studies are required for pyridinium. Also, studies on the full range of mammalian toxicity endpoints will need to be performed on pyridinium, although data for acute toxicity studies can be obtained from the dose range studies conducted for the repeat dose endpoint. Other endpoints for the other chemicals can be addressed by existing data, the

studies already proposed by the sponsor or by read-across approaches.

Specific questions or comments on the test plan and robust summaries are as follows:

1. Pyridine and pyridine derivatives are industrial solvents and chemical intermediates used in the production of drugs and vitamins as well as industrial products such as paints, dyes, rubber products and adhesives. They are also used in agricultural products, including a wide array of pesticides and plant growth regulators. Therefore, there is ample opportunity for environmental and human exposure although no data were provided on the magnitude of these exposures from the different uses of these substances.

2. A wide variety of toxic effects were observed, but these findings were inconsistent across proposed category members. Effects include male reproductive toxicity, olfactory lesions neurotoxic effects, hepatotoxicity, nephrotoxicity, cardiovascular toxicity and others. Thus, the test plan failed to show a common pattern of toxic responses for proposed category members. No information was provided on mechanism of action for any of the endpoints, other than some information on metabolism that failed to demonstrate common metabolites for the proposed members. The sponsor attempts to justify metabolic pathways (i.e., oxidation, conjugation, etc.) as relevant to category formation. It is important to note, however, that when two chemicals are acted on by the P-450 system, they may exhibit pronounced differences in patterns of toxicity.

3. The available data on ecotoxicity endpoints indicate wide differences in toxicity not accounted for by differences in bioavailability or biodegradation. Again, this argues against a single category for all nine chemicals. Moreover, the photodegradation half-lives range from 0.1 days to 163 days for those proposed category members with such data.

4. The sponsor states that piperidine is not carcinogenic, based on a 50-week bioassay. The bioassay duration for hazard identification is well-established at 104 weeks, so the 50-week study cannot be used to conclude lack of carcinogenicity.

5. If the sponsor wishes to pursue category designation for the pyridine derivatives, we recommend that gene array data be generated on the proposed members in a suitable in vitro or in vivo system. If proposed members cause the same pattern of changes on gene expression, then category justification would be more compelling.

Thank you for this opportunity to comment.

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